## REMARKS

The following remarks are submitted in response to the Office Action mailed on February 7, 2007. Claims 1, 15-17, 44, and 45 are currently pending and under consideration.

*Rejections Under 35 U.S.C. § 103*

Claim 1 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Holtzman (US Patent No. 5,969,123) in view of Schatz (US Patent No. 5,932,433). Specifically, the Examiner asserts that Holtzman teaches a biochip comprising a biotinylated receptor protein immobilized via a factor capable of specifically binding to biotin, wherein the receptor protein comprises a biotinylation sequence motif. However, the Examiner acknowledges that Holtzman fails to teach the biotinylation of the receptor protein carried out within a bacterial host. Rather, the Examiner asserts that Schatz teaches a recombinantly expressed biotinylated receptor protein immobilized via a factor capable of specifically binding to biotin, wherein the receptor protein comprises a biotinylation sequence motif, and wherein the biotinylation of the receptor protein has been carried out within a bacterial host instead of in vitro. The Examiner concludes that it would have been obvious to the skilled artisan to utilize a receptor protein biotinylated *in vivo*, as taught by Schatz, in the chip described by Holtzman, in order to provide a protein that has been biotinylated.

Dependent claims 15 and 16 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Holtzman in view of Schatz further in view of Tall (US Patent No. 6,756,228). The Examiner cites Holtzman and Schatz for the teachings described above and further cites Tall for teaching a LOX-1 receptor immobilized to a substrate in order to detect the presence of LOX-1 activity. The Examiner asserts that it would have been obvious to include LOX-1, as taught by Tall, as the receptor protein of Holtzman in view of Schatz, in order to provide a substrate that indicates susceptibility to atherosclerosis.

Dependent claims 17 and 44 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Brigham-Burke (US Patent No. 5,395,587) in view of Holtzman further in view of Schatz. The Examiner asserts that Brigham-Burke teaches a protein immobilized on a SPR substrate, but fails to teach the protein being biotinylated and immobilized via a factor that binds biotin. Rather, the Examiner asserts that Holtzman in view of Schatz, as applied to claim 1 above, teach a receptor protein immobilized on a substrate via a factor capable of specifically binding to biotin, and it would, therefore, have been obvious to the skilled artisan to include on the substrate of Brigham-Burke a biotinylated receptor protein as taught by Holtaman in view of Schatz.

Dependent claims 17 and 45 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Muramatsu (Analytical Chemistry, vol. 59, pp. 2760-2763, 1987) in view of Holtzman and further in view of Schatz. The Examiner asserts that Murumatsu teaches a protein immobilized on a crystal oscillator, and that Holtzman in view of Schatz teaches, as applied to claim 1, teach a biotinylated receptor protein immobilized on a substrate via a factor capable of specifically binding to biotin. Thus, the Examiner concludes that it would have been obvious to the skilled artisan to include on the substrate of Muramatsua biotinylated receptor protein immobilized by a factor capable of binding specifically to biotin as taught by Holtzman in view of Schatz.

Applicants respectfully traverse this basis of rejection and submit that the presently claimed receptor chip, on which a recombinantly expressed biotinylated receptor protein is immobilized via a factor capable of specifically binding to biotin, wherein the receptor protein comprises a biotinylation sequence motif, wherein the biotinylation of the receptor protein has been carried out within a bacterial host, and wherein the receptor protein has the ability of being specifically bound by a ligand of the receptor protein, is not obvious over any of the cited references, alone or in any cited combination.

Applicants note that each of the above cited combinations of references relies upon Holtzman in view of Schatz to teach a receptor chip on which a recombinantly expressed biotinylated receptor protin is immobilized via a factor capable of specifically binding to biotin, wherein the receptor protein comprises a biotinylation sequence motif, wherein the biotinylation of the receptor protein has been carried out within a bacterial host, and wherein the receptor protein has the ability of being specifically bound by a ligand of the receptor protein. The other references are cited merely as teaching additional limitations present in dependent claims. Accordingly, a demonstration that Holtzman in view of Schatz fails to render obvious the receptor chip of claim 1 necessarily leads to the failure of any other cited combination of references to render obvious other specifically claimed embodiments of these receptor chips.

Applicants respectfully submit that the combination of Holtzman in view of Schatz fails to establish a *prima facie* case of obviousness of the receptor chip of claim 1, since these references would fail to motivate the skilled artisan to produce the claimed receptor chip with any reasonable expectation of success. In addition, even assuming *arguendo* that Holtzman and Schatz taught or suggested the claimed receptor chip, Applicants submit that the claimed receptor chip provides surprising and unexpected benefits, *i.e.*, a superior chip, which would not have been expected in view of Holtzman and Schatz.

Applicants note that in order to establish obviousness, the invention must be considered as a whole. With respect to the presently claimed receptor chip, it is the combination of (i) production of *in vivo* biotinylated protein produced by inclusion bodies; and (ii) refolding these proteins in a particular orientation on a solid substrate that results in the claimed receptor chills. Producing functional, refolded proteins that can be oriented identically due to in vitro biotinylation in an amount sufficient to produce receptor chips had not been achievable prior to the disclosure of the instant application (as described on page 3, line 31, to page 4, line 8). Furthermore, the prior art references fail to teach that this could be possible.

Specifically, Schatz does not teach that a protein that has been biotinylated *in vivo* can maintain its natural activity, which is required by the instant claims (as the biotinylated

proteins of the instant claims are required to have the ability of being specifically bound by their ligands). This is clear from the description Schatz provides of potential uses of the *in vivo* biotinylated proteins described therein. On column 14, lines 10-16, Schatz states, "*[f]or instance, one could use the biotinylation peptides of the invention to purify BirA protein or other biotinylation enzymes. The peptides of the invention can serve as the substrate in an assay to screen for the presence of novel biotinylation enzymes.*" Thus, it is clear that the proteins biotinylated (either *in vivo* or *in vitro*) in Schatz are intended to be used only with respect to the biotinylation motif of the protein, and not the remaining protein. Thus, the key concept of the present invention, *i.e.*, normal use of the protein bound to a receptor chip by biotin, is not taught or suggested in Schatz. Therefore, the skilled artisan would not be motivated by Schatz to utilize an *in vivo* biotinylated receptor protein when desiring to produce a chip comprising a receptor protein capable of binding to its ligand.

In addition, Schatz does not teach or suggest that proteins that are traditionally difficult to express in high amounts, such as receptor proteins, can be successfully adapted to an *in vitro* biotinylation and expression protocol. Applicants also emphasize that Schatz describes the expression of MBP in E. coli, and MBP is naturally produced in *E. coli*. In contrast, prufiied receptor proteins are known to be difficult to produce using *in vivo* expression techniques, in part due to their propensity to accumulate within membranes. Thus, the skilled artisan would not be motivated by Schatz teaching the recombinant production of a natural *E. coli* non-receptor protein to produce *in vivo* a biotinylated receptor protein.

Furthermore, as noted above, the presently claimed receptor chip offers surprising advantages over the prior art, which further establishes that they are not obvious. Schatz does not teach any advantages associated with *in vivo* biotinylation in contrast to *in vitro* biotinylation, and suggests that these are simply alternatives. This is clear from column 14, lines 14-16, which state "*[t]he biotinylation reaction can occur in vivo (where few other proteins are naturally biotinylated) or in vitro, with readily available materials.*" Indeed, Schatz only describes the *in vivo* biotinylation of MBP, and never examines whether the biotinylated MBP can still bind

maltose. In contrast, the instant specification has demonstrated that *in vivo* biotinylation is extremely advantageous for the presently claimed receptor chips, since the receptor proteins are biotinylated at a particular motif and, therefore, are all immobilized on the substrate in the same orientation, which permits binding to substrate. Thus, the present receptor chip, which comprises immobilized *in vivo* biotinylated and expressed receptor proteins provides surprising advantages over the prior art, including reproducibility of binding to the chip and ability to bind to ligands.

In view of the above comments, Applicants submit that the receptor chip claimed in claim 1 is not obvious over the combination of Holtzman and Schatz. Based upon the teachings of these references, the skilled artisan would not be motivated to substitute an in vivo biotinylated and expressed receptor protein for the *in vitro* protein described by Holtzman. In addition, the presently claimed receptor chips offer unique and surprising advantages, which could not have been expected in view of the teachings of the prior art. As such, a finding of obviousness of the claimed receptor chips could only be bases upon impermissible hindsight analysis based upon the teachings of the instant specification.

Furthermore, Applicants submit that since the primary combination of references, namely Holtzman and Schatz, fail to render the receptor chip of claim 1 obvious, the receptor chips further defined in the remaining dependent claims are also non-obvious over any of the other cited combinations of references. None of these references remedy the deficiencies of Holtzman and Schatz with respect to motivating the skilled artisan to achieve the presently claimed receptor chips, comprising *in vivo* biotinylated and expressed receptor proteins. In addition, none of the additional references, or combinations thereof, teach or suggest the surprising advantages of the presently claimed receptor chips. Accordingly, all claims are non-obvious over all cited references, alone or in any combination.

In view of the above remarks, Applicants respectfully request that the Examiner reconsider and withdraw these bases of rejection.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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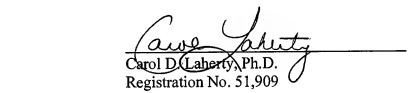

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